

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte DAVID E. LEVY, JOAN E. DURBIN,
ADOLFO GARCIA-SASTRE and PETER PALESE

Appeal No. 2002-1299
Application No. 08/962,740

ON BRIEF¹

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U.S. PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Before WILLIAM F. SMITH, ADAMS and MILLS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-5 and 35-37, which are all the claims pending in the application.

Claims 1, 35 and 36 are illustrative of the subject matter on appeal and are reproduced below:

1. An immortalized mammalian cell line homozygous for a Stat1 null allele
35. The immortalized mammalian cell line of Claim 1, wherein viral tropism of said cell line has been altered to be permissive for viral

¹ Appellants waived their request for Oral Hearing. Accordingly, we considered this appeal on Brief.

growth relative to that of the same cell line with wild type alleles of Stat1.

36. The immortalized mammalian cell line of Claim 35, wherein the cells of said cell line are fibroblast cells capable of producing influenza virus at from about 103 to about 106 PFU/ml at about two days after having been infected.

The references relied upon by the examiner are:

Leder et al. (Leder)	5,087,571	Feb. 11, 1992
Jallat et al. (Jallat)	5,814,716	Sep. 29, 1998

Todaro et al. (Todaro), "Quantitative Studies of the Growth of Mouse Embryo Cells in Culture and Their Development Into Established Lines," J. Cell. Bio., Vol. 17, pp. 299-313 (1963)

Durbin et al. (Durbin), "Targeted Disruption of the Mouse Stat1 Gene Results in Compromised Innate Immunity to Viral Disease," Cell, Vol. 94, pp. 443-50 (1996)

GROUND OF REJECTION

Claims 1-5 and 35-37 stand rejected under 35 U.S.C. § 103 as being unpatentable over Durbin in view of Jallat, Leder and Todaro.

CLAIM GROUPING

Appellants set forth the following three claim groupings: (1) claims 1-5 and 37; (2) claim 35 and (3) claim 36. Accordingly claims 35 and 36 stand or fall alone. Since all the claims of group (1) stand or fall together, we limit our discussion to representative independent claim 1. Claims 2-5 and 37 will stand or fall together with claim 37. In re Young, 927 F.2d 588, 590, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991).

DISCUSSION

According to the examiner (Answer, page 3), Durbin teach "the production of a Stat1 null allele vehicle capable of producing high titers of viruses." In this

regard, we note that the vehicles taught by Durbin are embryonic stem cells and transgenic mice. See Durbin, bridging paragraph, pages 443-444. The examiner explains (Answer, page 3), Stat1

is a gene product which interacts with interferon to change the viral tropism of the cell containing the Stat1, i.e. places the cells in an antiviral state. Therefore, a cell or cell line which does not produce the Stat1 product, i.e. a null allele, would be more susceptible to viral infection and replication thus being a good vehicle for viral production.

According to the examiner (Answer, bridging paragraph, pages 3-4), while "Durbin speaks to the development and utility of cell lines with such an allele ... [the reference] does not teach developing a cell line from the mice."

To make up for the deficiency in Durbin, the examiner relies on Leder, Jallat and Todaro. According to the examiner (Answer, page 4), Leder, Jallat and Todaro teach the production of cell lines from transgenic mice.

Claim 1:

In response to the rejection of record, appellants argue (Brief, page 4):

Durbin does not disclose or suggest making an immortalized Stat1 deficient cell line. ... Durbin never discloses or suggests any reason to prepare an immortalized Stat1-deficient cell line. Thus, Durbin clearly does not suggest an immortalized Stat1-deficient cell line or the utility of such immortalized cell line as hosts for producing viral stocks, for producing recombinant viral vectors, or for detecting viruses and the like.

In addition, appellants argue (id.), "Leder, Jallat and Todaro, do not remedy the deficiencies of Durbin as none of these references relate to Stat1-deficient transgenic animals or cell lines." According to appellants (Brief, page 5), "[t]he question here is not whether the cell line of the Stat1-deficient mouse disclosed

in Durbin could be immortalized, but whether one would have been motivated to perform such immortalization of Durbin's Stat1-deficient cell line based on Jallat, Leder, and Todaro, as suggested by the Examiner." In this regard, appellants argue (id.), "[t]he mere existence of Stat1-deficient mice cannot be a suggestion to make immortalized Stat1-deficient cell lines. The Examiner must show that the references render the claimed invention prima facie obvious, not simply a general method of making immortalized cells."

In response, the Examiner finds (Answer, page 5), the combination of references relied upon "provide motivation to make immortalized cell lines from the Durbin mouse as an easier vehicle to study the interactions of cytokines and Stat1 proteins. Immortalized cell lines can be readily multiplied and grown to run a plethora of assays much more quickly than the mouse itself." In this regard, we note "[t]he test for obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." In re Rosselet, 347 F.2d 847, 851, 146 USPQ 183, 186 (CCPA 1965).

As we understand the references, Durbin teach (page 443, column 2), "a wide range of cytokines, growth factors, and other signaling molecules, acting through a variety of receptor systems, have been shown to activate STAT1 in cell culture systems." As appellants point out (Brief, page 3), with regard to "a previously described Stat1 deficient cell line, Durbin states that, 'the lack of responsiveness of the parental cell line to other cytokines, and the

uncharacterized nature of the Stat1 defect have made generalizations concerning Stat1 function difficult to draw.” Therefore, “[t]o investigate further the generality of STAT1 involvement in cytokine signaling and to probe the roles of STAT1-linked pathways under physiologic settings and during development, [Durbin] ... disrupted the gene for STAT1 in embryonic stem (ES) cells and in mice.”

Therefore, to the extent that appellants would argue that Durbin should be limited to the study of Stat1 in vivo we do not agree. Not only does Durbin discuss earlier studies performed with cell lines (page 443), Durbin study Stat1^{-/-} ES cells and produce Stat1^{-/-} animals. We also note Durbin’s discussion of the difficulty in maintaining homozygous Stat1^{-/-} animals. (Durbin, page 445, column 2, “no homozygous animal born in this initial colony has survived greater than 8 weeks ... [however] Stat1^{-/-} animals obtained in ... [a pathogen-free] colony displayed no symptoms of spontaneous disease.”). In contrast, the examiner points out (Answer, page 5), immortalized cell lines are “an easier vehicle to study the interactions of cytokines and Stat1 proteins. Immortalized cell lines can be readily multiplied and grown to run a plethora of assays much more quickly than the mouse itself.” We note that the examiner’s comments are supported by Leder. Leder, column 3, lines 50-60.

In disclosing a method for providing a cell culture from a transgenic non-human mammal, Leder state (id.):

The animals of the invention can also be used as a source of cells for cell culture. Cells from the animals may advantageously exhibit desirable properties of both normal and transformed cultured cells;

i.e., they will be normal or nearly normal morphologically and physiologically, but can, like cells such as NIH 3T3 cells, be cultured for long, and perhaps indefinite, periods of time. Further, where the promoter sequence controlling transcription of the oncogene sequence is inducible, cell growth rate and other culture characteristics can be controlled by adding or eliminating the inducing factor.

According to the examiner (Answer, page 4), "[t]he desire to immortalize useful cell lines in order to confer extended usefulness is clear motivation to one of ordinary skill in the art and the techniques to do so are notoriously old and well known (this does not appear to be disputed by applicant)." In support of the examiner's position we note that Durbin point out (page 443, column 1), "[c]hemically mutagenized human fibrosarcoma cells defective in STAT1 have been isolated and used to demonstrate the requirement for STAT1 in IFN responses...." We also note that Jallat provide two methods of preparing mice from which immortalized cell-lines can be obtained. See column 3, lines 43-64. Accordingly, we agree with the examiner that based on the combination of prior art relied upon, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to have an immortalized mammalian cell line homozygous for a Stat1 null allele.

We recognize that we have discussed the Jallat and Leder references more extensively than the examiner. It is, however, well established that references are considered in their entirety for what they fairly suggest to one skilled in the art. In re Wesslau, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965) (the reference is considered in its entirety for what it fairly suggests to one skilled in the art). Therefore, based on the evidence of record, it is our opinion

that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to produce an immortalized cell line homozygous for a Stat1 null allele. Accordingly, we affirm the rejection of claim 1 under 35 U.S.C. § 103 as being unpatentable over Durbin in view of Jallat, Leder and Todaro. As discussed supra claims 2-5 and 37 fall together with claim 1.

Claim 35:

According to appellants (Brief, page 6), the combination of references relied upon "fail to suggest that viral tropism of such an immortalized cell line is permissive for viral growth relative to that of the same cell line with wild type alleles of Stat1. However, as the examiner explains (Answer, page 3), Stat1

is a gene product which interacts with interferon to change the viral tropism of the cell containing the [sic] Stat1, i.e. places the cells in an antiviral state. Therefore, a cell or cell line which does not produce the Stat1 product, i.e. a null allele, would be more susceptible to viral infection and replication thus being a good vehicle for viral production.

Durbin (page 445, column 2) supports the examiner's position, wherein Durbin report, "virus replicated to extremely high titers in Stat1^{-/-} animals while Stat1^{+/+} animals eliminated the virus within 2 days (Table 1)." Stated differently, Durbin report that the viral tropism of the Stat1^{-/-} animal was altered to be permissive for viral growth relative to a Stat1^{+/+} animal (the same animal with wildtype alleles of Stat1). There is no evidence of record that would suggest that a cell line derived from a Stat1^{-/-} animal would not be expected to exhibit the same degree of viral tropism as the animal from which the cell was derived. Accordingly, we are not

persuaded by appellants' argument. Therefore we affirm the rejection of claim 35 under 35 U.S.C. § 103 as being unpatentable over Durbin in view of Jallat, Leder and Todaro.


Claim 36:

Claim 36 stands on a different footing. As appellants explain (Brief, page 6), the combination of references relied upon "fail to suggest that fibroblast cells from the claimed immortalized cell line are capable of producing influenza virus at from about 10^3 to about 10^6 PFU/ml at about two days after having been infected." The examiner responds arguing (Answer, page 6), "[t]he claimed limitation is merely an inherent property of the cell line and thus the cells of the Durbin mouse." The claimed cell line, however, are fibroblast cells. While it may have been obvious from the combination of references relied upon to establish an immortalized cell line from a transgenic mouse homozygous for a Stat1 null allele, there is no motivation in the prior art of record directing one of ordinary skill in the art to select fibroblast cells. Accordingly, we reverse the rejection of claim 36 under 35 U.S.C. § 103 as being unpatentable over Durbin in view of Jallat, Leder and Todaro.

No time period for taking any subsequent action in connection with this
appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART


William F. Smith
Administrative Patent Judge


Donald E. Adams
Administrative Patent Judge


Demetra J. Mills
Administrative Patent Judge

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